754 Adrenergic Activity and Beta Blockade in Heart Failure

Tuesday, March 26, 1996, 2:00 p.m.–3:30 p.m.
Orange County Convention Center, Room 222

2:00

754-1 Low Level Physical Training Improves Peak Oxygen Consumption in Patients With Congestive Heart Failure Despite Long Term Beta Adrenergic Blockade by Enhancing Vascular Conductance and Growth

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In the absence of beta adrenergic blockade (BAB), 12 weeks of low level physical training (PT) at a workload corresponding to ≤50% of peak oxygen consumption (VO2) has been shown to increase peak VO2 in patients with congestive heart failure (CHF). In normal subjects, BAB attenuates the benefits of PT by preventing cardiac and skeletal muscle adaptations that contribute to increasing maximum VO2. Accordingly, 10 patients with CHF on long term therapy with ACE inhibitors, digoxin, loop diuretics, and BAB (rest and peak heart rates 64/min and 118/min) underwent 12 weeks of low level PT. Peak VO2 (ml/min/kg) and calf peak hyperemic response by plethysmography (CPHR, ml/min/100 ml) were measured at baseline (BL) and after 12 weeks of low level PT. Gene expression of vascular endothelial growth factor (VEGF) was quantified by competitive PCR on reverse transcribed mRNA obtained from vastus lateralis muscle biopsies at BL and 12 weeks. VEGF was normalized to glyceraldehyde-3-phosphate dehydrogenase, and expressed as a fold increase from BL.

	Peak VO2	CPHR	VEGF
BL	13.8	18.4	–
12 weeks	17.4*	26.3*	3–7

*$p < 0.05$ vs BL

Conclusion: In patients with CHF on long term BAB, low level PT substantially increases 1) peak VO2, 2) CPHR and gene expression of VEGF. Enhanced vasodilatory capacity and angiogenesis in the skeletal muscle beds appear to mediate the improvement in peak VO2 induced by low level PT in these patients.

2:15

754-2 Amiodarone Produces Effects Similar to β-Blockers in CHF

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Although amiodarone (AMIO) did not reduce total or sudden death mortality in the recently published CHF-STAT trial, there was a favorable trend ($p = 0.07$) in patients with a non-ischemic etiology (NI) of CHF. Evidence of greater efficacy in NI patients has also been noted with β-blockers in CIBIS and other smaller studies, and the most impressive results have been improvement in LV function and prevention of endpoints related to progressive CHF rather than sudden death. Since AMIO has β-blocking activity, the present analyses were undertaken to determine whether it produces similar functional and endpoint changes, and whether these effects occur primarily in NI patients. In CHF-STAT, 674 patients with NYHA class 2–4 CHF (71% ischemic, 29% NI) and LV EF < 40% were randomized to AMIO or placebo. At 6 mos, there was a greater increase in LV EF on AMIO (8.1 ± 10.2 vs 2.6 ± 7.8 EF units, $p < 0.001$), but this was significantly greater in NI than CAD patients (12.3 ± 11 vs 6.6 ± 2.1 units). The change in EF was inversely related to change in heart rate. An improvement in EF ≥ 5% was associated with an improvement in survival in the NI group ($p < 0.001$), but not in CAD patients. In NI patients, AMIO was associated with reductions in hospitalizations for CHF (RR 0.56, [0.31–1.02], $p = 0.06$), CHF deaths plus CHF hospitalizations (RR 0.49 [0.28–0.85], $p = 0.01$), and cardiac deaths plus CHF hospitalizations (RR 0.56 [0.36–0.87], $p = 0.01$). None of these endpoints was affected in CAD patients (RR 0.93–0.95). These results demonstrate that AMIO increases LV EF, particularly in NI cardiomyopathy. These changes are associated with improvement in clinical outcomes, especially those related to progressive CHF, in NI patients but not in those with CAD. This profile of effects is very similar to those observed with β-blockers in CHF.

2:30

754-3 Effects of Carvedilol on Cardiovascular Hospitalizations in Patients With Chronic Heart Failure

Michael B. Fowler, E. Michael Gilbert, Jay N. Cohn, Michael A. Bristow, Wilson S. Colucci, Neil H. Shusterman, Milton Packer for the Carvedilol Heart Failure Study Group. *Stanford University, Stanford, CA*

Carvedilol (C), a nonselective β-adrenergic blocking drug with vasodilating and antioxidant effects was recently compared to placebo (P) in a trial program consisting of 4 multicenter, randomized double-blind studies run concurrently across the U.S. 1094 patients with NYHA II–IV heart failure (and LVEF < 35%) were randomized to receive treatment for 6–12 months. To evaluate the effect of C on hospital admissions, data on all hospitalizations were prospectively obtained throughout the study period, and analyzed according to protocol for patients who completed 2 months of maintenance therapy (588 patients on C, 334 on P).

Carvedilol therapy was associated with a 38% (95% CI: 0.149, 0.542; $p = 0.003$, Cochran-Mantel-Haenszel) reduction in risk of hospitalization (for all cardiovascular reasons). Hospitalization for heart failure was reduced by 47% (95% CI: 0.135, 0.673; $p = 0.011$). Hospitalization for MI occurred in 0.3% of patients randomized to C compared to 1.2% in the P group ($p = 0.067$).

A decrease in the duration of the hospital stay by 1.3 days (95% CI; 0.3, 2.2; $p = 0.009$, analysis of variance) was also seen in the patients treated with C. No differences were observed for cardiovascular hospitalizations (CV) or hospitalizations for CHF among the subgroup analyses for baseline characteristics of age, sex, race, NYHA class, LVEF, history of MI and etiology of disease.

In conclusion, carvedilol provides a substantial clinical benefit to patients with class II-IV heart failure by reducing the risk of all CV hospitalizations by 38% and hospitalizations for CHF by 47%. The duration of hospital stay was also shorter in patients receiving carvedilol. The reduction in hospitalizations observed is concordant with the mortality benefit reported in patients treated with carvedilol.

2:45

754-4 Effect of Carvedilol in Severe Chronic Heart Failure

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Carvedilol (C), a β-blocker with vasodilating properties via α_1-blockade, was evaluated in patients with severe chronic heart failure (CHF) [ejection fraction (EF) ≤ 0.35, NYHA III/IV] in a double-blind, placebo-controlled trial of 6 months duration. The protocol was stopped early upon recommendation of the Data and Safety Monitoring Board to terminate Phase III clinical trials in light of a survival advantage of C. One-hundred five of a planned 140 patients on standard therapy (diuretics, digoxin, and ACE-I) and unable to walk 350 m in 6 min were randomized to receive maximally tolerated C (n = 70) up to 25 mg bid or placebo (P; n = 35). Parameters evaluated included change in quality of life (Minnesota Living with Heart Failure Questionnaire), patient/physician global assessment and EF. Analyses (at end-point) were limited to 40 patients on C and 21 on P, due to truncation of the study.

Results: Patients receiving C had a greater increase in EF at 6 months compared to P (+0.09 vs +0.02; $p = 0.004$). Clinical benefit was evidenced by improvement in the global assessment by patients in 88% on C vs 67% on P ($p = 0.032$), and by physicians in 83% vs 52% ($p = 0.023$). Only 3% of patients/physicians reported worsening on C, whereas 19% patients and 15% physicians reported worsened CHF on P. Two deaths (2.9%) occurred on C and two (5.7%) on P. Several other measures of efficacy favored C without reaching statistical significance, including change in quality of life score (+12 C; +9 P), 6-min walk distance (299.9 m on C, 278.3 m on P), improvement in NYHA Class (23% C vs 19% P). Hospitalizations for worsening CHF occurred in 7.5% of patients on C, and 4.8% on P.

Conclusion: The addition of carvedilol to diuretics, digoxin and ACE-I therapy in patients with severe CHF results in an improvement in EF and reduced risk of clinical deterioration. These data are concordant with the hemodynamic and clinical benefits observed in patients with less severe CHF treated with carvedilol.

3:00

754-5 Carvedilol Reduces Left Ventricular Volumes in Patients With Heart Failure of Ischemic Etiology

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Beta-blocker therapy has been shown to increase left ventricular ejection